Nkx2-5 regulates cardiac growth through modulation of Wnt signaling by R-spondin3.

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Public Summary:
The gene Nkx2.5 has been recognized to be important in heart development, although all of its functions have not been clarified. Separately, what are known as Wnt signals are also recognized to be important in heart development. In this study, it was found that one function of Nkx2.5 is to directly control expression of the Wnt agonist Rspo3 and thereby support Wnt signaling. This in turn controls the choice of progenitor cell behavior between proliferation and differentiation that results in proper heart morphogenesis. A number of congenital heart defects were observed when Nkx2.5, Rspo3, or related genes and processes were experimentally interrupted.

Scientific Abstract:
A complex regulatory network of morphogens and transcription factors is essential for normal cardiac development. Nkx2-5 is among the earliest known markers of cardiac mesoderm that is central to the regulatory pathways mediating second heart field (SHF) development. Here, we have examined the specific requirements for Nkx2-5 in the SHF progenitors. We show that Nkx2-5 potentiates Wnt signaling by regulating the expression of the R-spondin3 (Rspo3) gene during cardiogenesis. R-spondins are secreted factors and potent Wnt agonists that in part regulate stem cell proliferation. Our data show that Rspo3 is markedly downregulated in Nkx2-5 mutants and that Rspo3 expression is regulated by Nkx2-5. Conditional inactivation of Rspo3 in the Isl1 lineage resulted in embryonic lethality secondary to impaired development of SHF. More importantly, we find that Wnt signaling is significantly attenuated in Nkx2-5 mutants and that enhancing Wnt/beta-catenin signaling by pharmacological treatment or by transgenic expression of Rspo3 rescues the SHF defects in the conditional Nkx2-5(+/-) mutants. We have identified a previously unrecognized genetic link between Nkx2-5 and Wnt signaling that supports continued cardiac growth and proliferation during development. Identification of Rspo3 in cardiac development provides a new paradigm in temporal regulation of Wnt signaling by cardiac-specific transcription factors.